

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

To:
**HAMILTON, BROOK, SMITH
& REYNOLDS, P.C.**
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INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

Rec'd IFD

Date of mailing
(day/month/year)

07/03/2005

PAYMENT DUE

within 45 months from the above date of mailing

Applicant's or agent's file reference
3518.1015002International application No.
PCT/US2004/024725International filing date
(day/month/year)

30/07/2004

Applicant

DEPUY SPINE, INC.

1. This International Searching Authority

- (i) considers that there are 18 (number of) inventions claimed in the international application covered by the claims indicated ~~below~~ on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~ on the extra sheet:

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- (ii) has carried out a partial international search (see Annex) will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
see annex

- (iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby invited, within the time limit indicated above, to pay the amount indicated below:

EUR 1,550,00 x 17 = EUR 26,350,00
Fee per additional invention number of additional inventions total amount of additional fees

Or, _____ x _____ = _____

The applicant is informed that, according to Rule 40.2(c), the payment of any additional fee may be made under protest, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. Claim(s) Nos. see annex have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority
 European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Sylvia Hermier

C169
MAY 14 2005

HAMILTON, BROOK,
SMITH & REYNOLDS, P.C.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4,30,34-66,80-82 (partially) 5-11,67-75

Use of an inhibitor of a pro-inflammatory interleukin for the manufacture of a medicament for treating an inflamed orthopedic joint.

2. claims: 1-4,30,34-66,80-82 (partially) 12-15,76-79,83

Use of an inhibitor of TNF-alpha synthesis, an inhibitor of membrane-bound TNF-alpha or an inhibitor of a natural receptor of TNF-alpha for the manufacture of a medicament for treating an inflamed orthopedic joint.

3. claims: 1-4,30,34-65,80-82 (partially) 19-21

Use of an inhibitor of NO synthase for the manufacture of a medicament for treating an inflamed orthopedic joint.

4. claims: 1-4,30,34-65,80-82 (partially) 22

Use of an inhibitor of PLA2 enzyme for the manufacture of a medicament for treating an inflamed orthopedic joint.

5. claims: 1-4,30,34-65,80-82 (partially) 23-27

Use of an inhibitor of an anti-proliferative agent for the manufacture of a medicament for treating an inflamed orthopedic joint.

6. claims: 1-4,30,34-65,80-82 (partially) 28

Use of an anti-oxidant for the manufacture of a medicament for treating an inflamed orthopedic joint.

7. claims: 1-4,30,34-65,80-82 (partially) 31-33

Use of an apoptosis inhibitor for the manufacture of a medicament for treating an inflamed orthopedic joint.

8. claims: 1-4,30,34-65,80-82 (partially) 29

Use of an inhibitor of MMP for the manufacture of a medicament for treating an inflamed orthopedic joint.

9. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a diaryl imidazole for the manufacture of a medicament for treating an inflamed orthopedic joint.

10. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a diaryl N,N' diaryl urea or a N,N-diarylurea for the manufacture of a medicament for treating an inflamed orthopedic joint.

11. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a benzophenone for the manufacture of a medicament for treating an inflamed orthopedic joint.

12. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a pyrazole ketone for the manufacture of a medicament for treating an inflamed orthopedic joint.

13. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a indole amide for the manufacture of a medicament for treating an inflamed orthopedic joint.

14. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a diamide for the manufacture of a medicament for treating an inflamed orthopedic joint.

15. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a quinazoline for the manufacture of a medicament for treating an inflamed orthopedic joint.

16. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a pyrimido'4,5-d!pyrimidinone for the manufacture of a medicament for treating an inflamed orthopedic joint.

17. claims: 1-4,16,17,30,34-65,80-82 (partially)

Use of an inhibitor of p38 kinase wherein the compound is a pyridylamino-quinazoline for the manufacture of a medicament for treating an inflamed orthopedic joint.

18. claims: 1-4,30,34-65,80-82 (partially) 18

Use of an inhibitor of a 1-aryl-2-pyridinyl heterocycle as specified in claim 18 for the manufacture of a medicament for treating an inflamed orthopedic joint.

The problem to be solved by the present application is to provide for the treatment of inflamed orthopedic joints.

The proposed solution is to use a compound selected from

- i) an inhibitor of a pro-inflammatory interleukin;
 - ii) an inhibitor of TNF-alpha synthesis;
 - iii) an inhibitor of membrane-bound TNF-alpha,
 - iv) an inhibitor of a natural receptor of TNF-alpha,
 - v) an inhibitor of NO synthase;
 - vi) an inhibitor of PLA2 enzyme;
 - vii) an anti-proliferative agent;
 - viii) an anti-oxidant,
 - ix) an apoptosis inhibitor selected from the group consisting of EPO mimetic peptides, EPO mimetibodies, IGF-I , IGF-II, and caspase inhibitors,
 - x) an inhibitor of MMPs,
 - xi) an inhibitor of p38 kinase, said inhibitor being a
 - a) diaryl imidazole (sic)
 - b) N,N'-diaryl urea;
 - c) N,N-diaryl urea;
 - d) benzophenone;
 - e) pyrazole ketone;
 - f) indole amide;
 - g) diamides;
 - h) quinazoline;
 - 1) pyrimido'4,5-d!pyrimidinone
 - j) pyridylamino-quinazoline.
- or
- xii) a 1-aryl-2-pyridinyl heterocycle selected from the group consisting of:
 - a) 4,5 substituted imidazole;
 - b) 1,4,5 substituted imidazole;
 - c) 2,4,5 substituted imidazole;
 - d) 1,2,4,5 substituted imidazole; and
 - e) non-imidazole 5-membered ring heterocycle.

Said compounds may be administered trans-capsularly, closely adjacent to the outer wall of the capsule or at a location closely adjacent to an outer wall of the capsule. See claims 1, 47, 60.

US5368841 discloses local i.e. intracapsular injection of drugs for treating inflammatory joint conditions. See the passages cited in the search report.

US2001016195 discloses antagonists of IL-1, IL-6, IL-8 to treat osteoarthritis and other forms of arthritis including rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis. Said treatment comprises localized administration, including perilesional or intralesional administration of compounds including interleukin 1 receptor antagonist (IL-1 RA) (Amgen) and interleukin 1 receptor type II (IL-1R type II) (Immunex). See the passages cited in the search report.

WO0185179 discloses dextran based composition for injecting into damaged or diseased joints, filling cavities and spaces in artificial joints, applying to joints in connection with post-surgical procedures and injected into joint injury. See the passages cited in the search report.

EP438234 discloses the intrasynovial administration of antithrombin in relation to the treatment of arthritis. See the passages cited in the search report.

US4427649 discloses compsns. useful for treating rheumatoid inflammations of the synovial joints, since they can be injected directly into the cavity of the joint. See the passages cited in the search report.

US6294170 discloses the intracapsular administration of an inhibitor of IL-1, preferably IL-1ra, either alone or in combination with another drug for treating inflammatory joint diseases. See the passages cited in the search report.

Furthermore, the compounds of the proposed solutions do not share a significant structural element, nor do they belong to a same recognized class of chemical compounds.

According to Article 3(4)(iii) PCT, an international application shall comply with "the prescribed requirement of unity of invention". This means, as explained in Rule 13.1 PCT, that the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

From the above cited documents, it appears that the use of above specified compounds in relation to the treatment of above specified disorders is known in the prior art and can not fulfil the role of special technical feature (general inventive concept) in the sense of Rule 13.2 PCT.

Accordingly there is no new technical effect linking the different groups of inventions.

In the present application no further technical feature can be distinguished that can be regarded as a "special technical feature"

involved in the technical relationship among the different inventions.

Consequently the present application lacks unity of invention.

As searching the other inventions would have caused a major additional searching effort, only the first invention was searched.

The application relates to a plurality of inventions, or groups of inventions, in the sense of Rule 13.1 PCT. They have been divided as defined above. If the applicant pays additional fees for one (or more) not yet searched group(s) of invention(s), then the further search(es) may reveal further prior art that gives evidence of a further lack of unity '*a posteriori*' within one (or more) of the not yet searched group(s). In such a case only the first invention in this (each of these) group(s) of inventions, which is considered to lack unity of invention, will be the subject of a search. No further invitation to pay further additional fees will be issued. This is because Article 17(3)(a) PCT stipulates that the ISA shall establish the International Search Report on those parts of the international application which relate to the invention first mentioned in the claims ('main invention') and for those parts which relate to inventions in respect of which the additional fees were paid. Neither the PCT nor the PCT guidelines provide a legal basis for further invitations to pay further additional search fees (W17/00, point 11 and W1/97, points 11-16).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 3.

Although claims 1-83 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/28828 A (AMGEN BOULDER INC; COLLINS, DAVID, S; BEVILACQUA, MICHAEL, P) 14 August 1997 (1997-08-14) abstract page 5, line 23 – page 9, line 5 page 10, line 7 – page 11, line 29 page 55, line 3 – page 60, line 20 page 64, lines 4-19 page 75, lines 8-32; claims 1-37; examples 2-4 ----- WO 98/24477 A (AMGEN INC; BENDELE, ALISON, M; SENNELLO, REGINA, M) 11 June 1998 (1998-06-11) abstract; claims 1-6 page 1, lines 5-9 page 5, lines 5-13 page 6, line 23 – page 8, line 32 page 43, line 29 – page 45, line 22 ----- US 6 294 170 B1 (BOONE THOMAS C ET AL) 25 September 2001 (2001-09-25) abstract column 5, line 46 – column 6, line 14 column 27, line 4 – column 33, line 12 ----- -/-	1-11,30, 34-75, 80-82
X		1-11,30, 34-75, 80-82
X		1-11,30, 34-75, 80-82

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Annex Form PCT/ISA/206
COMMUNICATIONS RELATING TO THE RESULTS
OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/US2004/024725

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 133 995 A (THE UNIVERSITY OF COLORADO FOUNDATION, INC; AMGEN INC; SYNERGEN, INC) 19 September 2001 (2001-09-19) abstract paragraphs '0018!, '0021! - '0025! page 26, line 5 - page 35, line 7 -----	1-11,30, 34-75, 80-82
X	GABAY C: "IL-1 TRAP" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 4, no. 5, May 2003 (2003-05), pages 593-597, XP009017868 ISSN: 0967-8298 the whole document -----	1-11,30, 34-75, 80-82
X	DAYER J-M: "THE PIVOTAL ROLE OF INTERLEUKIN-1 IN THE CLINICAL MANIFESTATIONS OF RHEUMATOID ARTHRITIS" RHEUMATOLOGY, OXFORD UNIVERSITY PRESS, LONDON, GB, vol. 42, no. SUPPL 2, May 2003 (2003-05), pages II03-II10, XP008041555 ISSN: 1462-0324 the whole document -----	1-11,30, 34-75, 80-82
X	US 2001/016195 A1 (TOBINICK EDWARD L) 23 August 2001 (2001-08-23) abstract paragraphs '0002! - '0011! paragraphs '0018!, '0019! -----	1-11,30, 34-75, 80-82
X	US 5 368 841 A (TRAUNER ET AL) 29 November 1994 (1994-11-29) abstract column 5, lines 34-52 -----	1
X	WO 01/85179 A (CLEMSON UNIVERSITY) 15 November 2001 (2001-11-15) the whole document -----	1
X	EP 0 438 234 A (KITA, KIYOSHI) 24 July 1991 (1991-07-24) the whole document -----	1
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Patent Family Annex

Information on patent family members

 International Application No
 PCT/US2004/024725

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